Long-term transfusion of polymerized bovine hemoglobin in a Jehovah's Witness following chemotherapy for myeloid leukemia: a case report

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A 52-year-old female Jehovah's Witness presented with relapsed secondary acute myeloid leukemia. Because of chemotherapy-induced anemia, she was infused with the bovine hemoglobin (Hb)-based oxygen carrier HBOC-201 (Biopure) as the sole means of transfusion support. HBOC-201 has only been used for management of acute hemorrhage, and its utility in providing longer term transfusion support is unknown. Over a period of 18 days, a total dose of 1230 g of HBOC-201 was delivered. Although the patient succumbed to the disease after 18 days of treatment, this case documents our experience with the highest dose and duration of HBOC-201 ever used. Although possible renal toxicity could not be definitively excluded, the homogeneous extraction of oxygen by the brain in the presence of and perhaps from HBOC-201 was demonstrated.

ABBREVIATIONS: HBOC(s) = hemoglobin-based oxygen carrier(s); PET = positron emission tomography.

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Bovine hemoglobin (Hb)-based oxygen carriers (HBOCs) have been proposed to serve as an alternative to red cell (RBC) transfusions in the management of acute blood loss.[1] The main advantages of HBOC include: 1) the product does not require blood group typing or cross-matching before transfusion, 2) it has a long shelf life, and 3) the risk of transmission of viral or bacterial disease is low.[2] Owing to its short half-life, however, the utility of HBOC to support longer term tissue oxygenation as well as potential side effects remain largely unknown. We report the use of the bovine Hb-based oxygen carrier, HBOC-201 (Hemopure, Biopure, Cambridge, MA) to provide transfusion support for 18 days in a Jehovah's Witness who refused RBC and platelet (PLT) transfusions after chemotherapy for myeloid leukemia.

CASE REPORT

A 52-year-old female Jehovah's Witness (weight, 94.7 kg) was referred for management of her relapsed secondary acute myeloid leukemia, M4 subtype. On admission, her peripheral blood white cell (WBC) count was 1.2×10^9 per L and the differential count showed 87 percent blasts. Her Hb level was 7.2 g per dL, her RBC count was 2.2×10^{12} per L, and her PLT count was 53×10^9 per L. Her blood urea nitrogen and creatinine were within normal limits. After extensive discussions with the patient regarding her options, a decision was made to treat her with a dose-reduced, abbreviated 3-day course of mitoxantrone and etoposide together with antibiotics and 60,000 U of erythropoietin subcutaneously twice weekly, oxygen, and bed rest. By Day 8 after chemotherapy, she experienced extreme fatigue but continued to have an unremarkable physical examination. Transfusion of HBOC-201 was started. Each unit contained 30 g of Hb as described previously.[3] HBOC-201 was infused (Fig. 1) at a dose of 60 g per day for the next 7 days. Her subjective sensation of tiredness decreased; however, she still became fatigued upon minimal exertion. Her RBC counts continued to decline. Total Hb and plasma HBOC-201 was measured on a cell counter (Advia, Bayer Diagnostics, Tarrytown, NY)

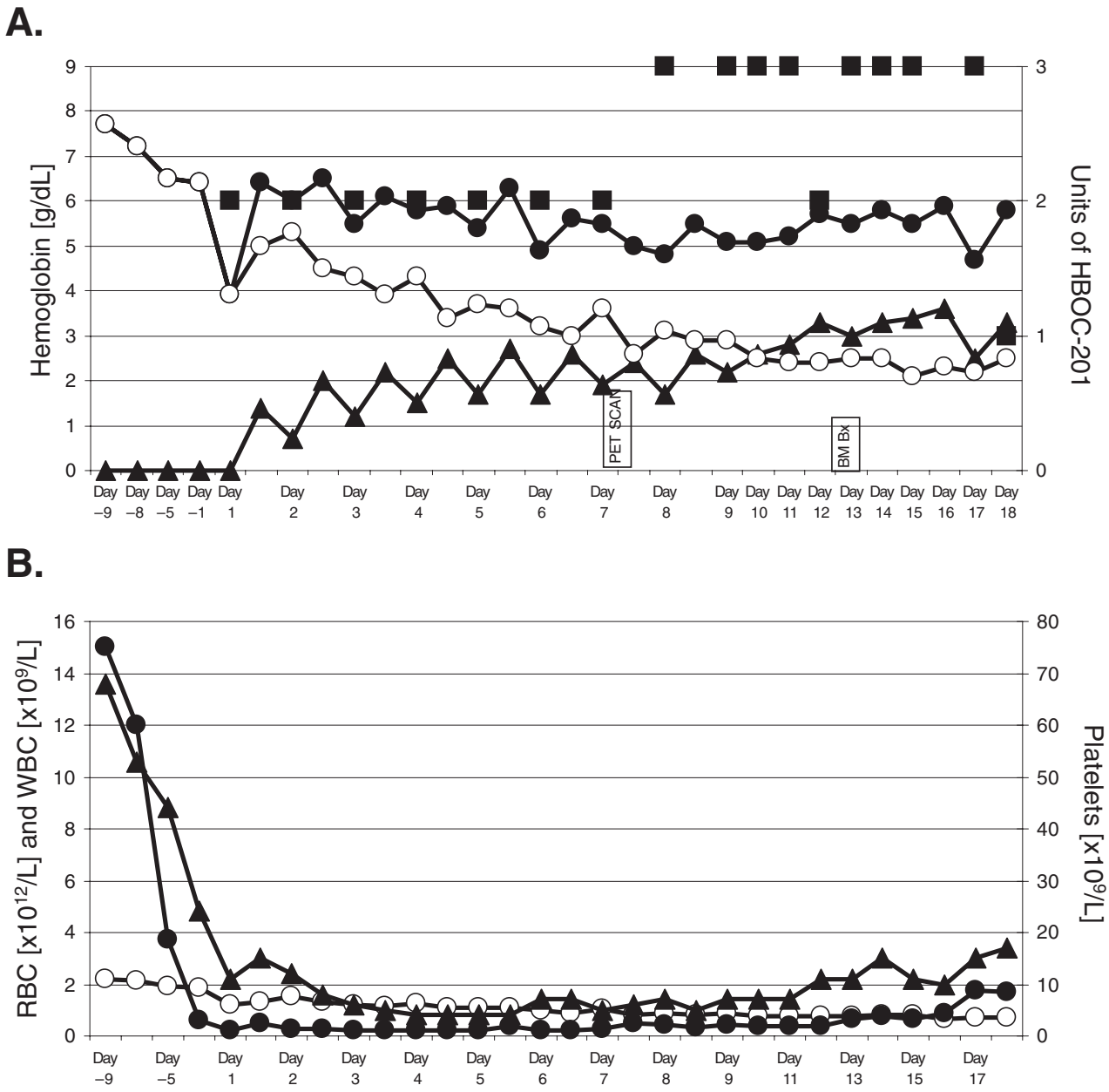

Fig. 1. Hematologic variables during administration of HBOC-201. (A) Concentrations of total Hb (●), bovine Hb (▲), and RBC Hb (○) in the patient's circulation. The first infusion of HBOC-201 occurred on Day 1. (■) HBOC-201 infusions and the number of infused units (each unit is the equivalent of 30 g of Hb). (B) The levels of the total WBCs (●), RBCs (○), and PLTs (▲) during patient's hospitalization. During the last 48 hours, WBC count and PLT count increased to 1.7×10^9 and 17×10^9 per L, respectively.

from anticoagulated whole blood. The total Hb minus the plasma HBOC-201 was used to calculate the patient's RBC-derived Hb level. On Day 7, there was clinical concern whether the continued decline in RBC counts (Fig. 1A) would affect cerebral oxygenation. An O-15 inhalation positron emission tomography (PET) scan was ordered as noninvasive pulse oximetry is not a reliable measure of oxygenation during HBOC-201 transfusion according to manufacturer's information. On Day 8 of HBOC-201 treatment, her RBC Hb level was 3.1 g per dL (Fig. 1A), and because of deterioration of her clinical status, it was decided to increase the HBOC-201 dose to 90 g per day. The next day (Day 9) she developed shortness of breath, and a chest X-ray revealed evidence of pulmonary edema, which required treatment with intravenous (IV) furosemide and a rebreather mask. Her pulmonary edema

prompted an echocardiogram performed on Day 11, which showed hypokinesis of the ventricles. Given these symptoms, we could not rule out the fact that the pulmonary edema may be due to a potential side effect of the blood substitute, and it was decided to reduce the dose of 60 g per day HBOC-201 on Day 12. On Day 13, she had an episode of chest pain requiring IV morphine. An electrocardiogram and creatine kinase enzyme profile, however, revealed no evidence of myocardial infarction. Because her RBC Hb concentration was now only 2.5 g per dL and she continued to clinically deteriorate, we decided to increase the HBOC-201 dose back to 90 g per day. On Day 15 she developed intermittent confusion and became oliguric. The urinalysis did not show free Hb and a renal ultrasound examination was normal. Her RBC count continued to decline while the WBC count increased (Fig. 1B). A marrow biopsy showed 32 percent blasts and abundant histiocytic cells with hemosiderin deposition (Fig. 2B). On Day 15, her HBOC-201 level peaked at 3.6 g per dL. It was decided to withhold HBOC-201 treatment on Day 15 and she was transferred to the intensive care unit. On Day 16 she required intubation for increasing tachypnea and underwent hemodialysis for progressive renal failure. She received 90 g of HBOC-201 throughout the day. The next day the patient's condition was unchanged, and she received 30 g of HBOC-201. During the day she had an episode of ventricular tachycardia; resuscitation was attempted, which was unsuccessful and the patient expired. In this patient a total of 41 units of HBOC-201 (1230 g [12.9 g/kg]) were administered as one 30-g, eight 60-g, and eight 90-g doses over an 18-day period. The mean hematocrit level during 18 days of HBOC-201 therapy was 10 percent. The mean total Hb concentration during the course of therapy was 5.5 g per dL, of which HBOC-201 comprised as much as 3.6 g per dL.

RESULTS AND DISCUSSION

This case provides novel information regarding critical issues in the long-term use of HBOC-201 without concomitant RBC support. These issues relate to maximum dosage, possible renal and pulmonary toxicity, and cerebral oxygenation.

Owing to the patient's religious preferences, this report describes the use of the highest total dose (1230 g) for the longest duration (18 days) of continuous HBOC-201 transfusion ever used. In comparison, a previous study used 330 g of HBOC-201 over 7 days to treat a patient with autoimmune hemolytic anemia.[3] A maximum plasma concentration of HBOC-201 of 3.36 g/dL was similar to the 3.6 g per dL that we observed on Day 15. The peak plasma HBOC-201 level of 3.6 g per deciliter represented more than 61 percent of total Hb.

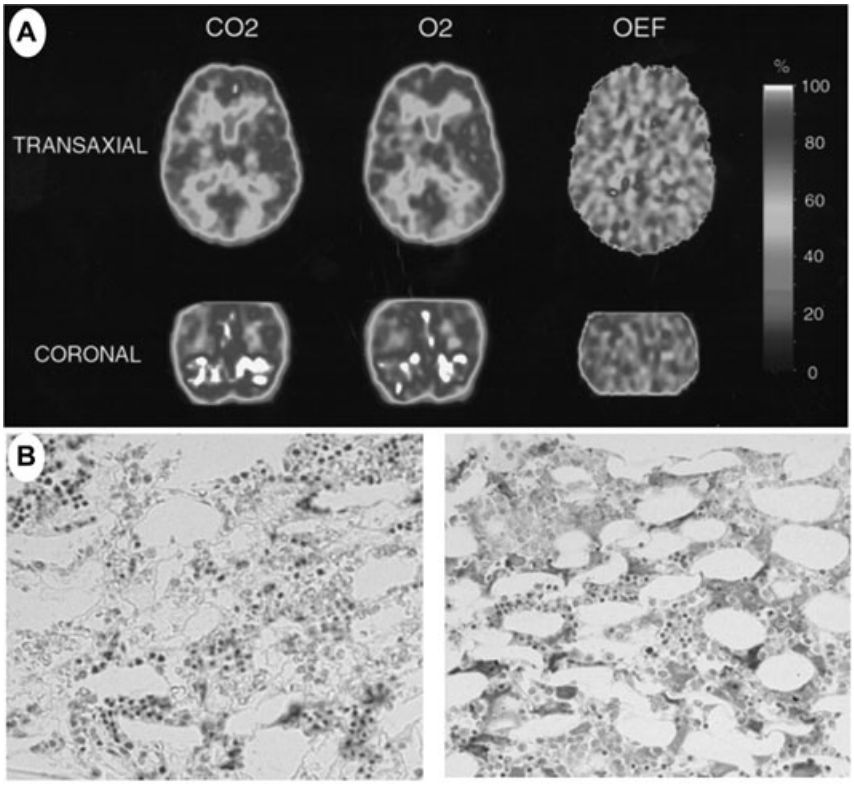

Fig. 2. Additional studies performed during patient hospitalization. (A) PET scan of the brain with ^{15}O was performed on Day 7. Homogenous oxygenation was observed. (B) Marrow biopsy was performed on Day 14 and showed significant accumulation of hemosiderin-laden macrophages (right panel) in comparison to marrow biopsy performed before treatment (left panel). The presence of free iron and free HBOC-201 in the tissue cannot be excluded. OEF = oxygen extraction fraction.

The patient became oliguric around Day 15 to Day 16 of transfusion. HBOC-201 is a glutamer (glutaraldehyde cross-linked to Hb) of bovine Hb.[3] It has not been associated with overt renal toxicity probably because cross-linked tetrameric Hbs and polymerized Hbs do not undergo glomerular filtration.[4] Cross-linked Hbs can, however, pass through the renal peritubular capillaries and appear in the interstitial fluid[4] and in tubular cells as seen by iron stains.[5] Thus although the renal failure was likely due to multiorgan failure, the possible toxic effects due to the chronic scavenging of nitric oxide by Hb in the renal interstitial tissues cannot be excluded.[6]

We could, however, document a markedly increased number of hemo-

siderin-laden macrophages in the marrow (Fig. 2B). The accumulation of macrophages to clear a perfluorochemical (Fluosol-DA) RBC substitute has been associated with a flu-like syndrome due to the release of cytokines and activation of complement.[7] Therefore, cytokine release may have been one potential mechanism contributing to our patient's clinical course. Our patient demonstrated a number of signs compatible with this scenario including lowered blood pressure and multiorgan failure. Blood cultures were obtained, but did not reveal any evidence of bacterial growth.

We have shown by PET scan that the brain was able to extract oxygen in the presence of, and perhaps from, HBOC-201. This is the first documentation of the bilaterally similar and homogeneous extraction of oxygen in the presence of soluble HBOC-201 by the brain tissue (Fig. 2A). PET scan techniques documenting the quantitative extraction of oxygen in tissues perfused by soluble Hbs have been studied in mice.[8] Because of the risks of placing an arterial line in this patient, we were unable to perform quantitative measurements of oxygen extraction by the brain.

This patient illustrates complex issues related to management of patients with hematologic malignancy who do not accept blood components. HBOC-201, though shown to be effective when used in emergency situation in other trials,[1] may not be useful as a sole oxygen-carrying component in anemia due to myelosuppressive therapy.

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